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PROBLEMS OF MEASUREMENT AND INTERPRETATION WITH REINFORCING BRAIN STIMULATION[1]

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An increasing number of experiments have been concerned with various aspects of reinforcing brain stimulation. The dramatic nature of many of the findings, however, has often forced methodological and interpretive problems into the background. The present paper discusses some of the problems encountered in: (a) measuring the reinforcement strength, (b) determining stimulus thresholds, (c) interpreting interactions between specific neural areas.

The discoveries that electrical stimulation of the brain may have positive and negative reinforcing properties have triggered experimentation and speculation which have been increasing at a rapid rate.[2] The possibility that the road was now open to the discovery of basic physiological mechanisms of motivation and emotion aroused the active interest of psychologists, physiologists, pharmacologists, anatomists, and others. Because of the interdisciplinary nature of much of the research and in part because the dramatic nature of the findings tended to force questions of methodology into the background, many of the complexities of the methods adopted have not been fully appreciated. As there have been a number of attempts in recent years to integrate experimental findings into theoretical schemes, it would seem appropriate at this time to examine some of the problems of measurement and interpretation of the results obtained with reinforcing brain stimulation.

In emphasizing the problems of measurement and the determination of what has been measured there is no intent to restrict exploration, but rather to locate buoys which point out where there is a risk of running aground. If more attention is not given to these problems there is the danger of being overwhelmed by an accumulation of anecdotal reports which will seriously impede progress in this field.

Although there may be many ways of organizing a discussion of the problems of measuring and interpreting the reinforcing consequences of brain stimulation, the major issues can be conveniently, if somewhat arbitrarily, grouped under three headings: (*a*)

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[2] For a comprehensive review the reader is referred to Olds, 1962.

[redacted]cement strength, [redacted] and (c) [redacted] between specific [redacted] areas.

Measuring Reinforcement Strength

Following the initial demonstration that animals would respond in order to obtain electrical stimulation of certain brain areas, it soon became apparent that methods to quantify the strength of the reinforcement were needed. Studies of the relative reinforcement strength of stimulation of different neural areas and estimates of change in reinforcement value with different stimulus parameters, drugs, ablations, gonadectomy, and deprivation have been the subjects of numerous studies (see Olds, 1962). These studies all require methods of determining change in the reinforcement properties of brain stimulation.

The most widely used measure of the strength of a reinforcer is the rate of making some response (usually lever pressing) which is followed by the presentation of that reinforcer. In addition to the convenience of this measure there is much appeal in the argument that the length of time permitted to elapse between responses reflects the intensity of the desire for the reward. There are difficulties, however, of both an empirical and logical nature. Empirically, it has been shown that response rate can be a misleading index of reinforcement with brain stimulation as results may not agree with an animal's preference (Hodos & Valenstein, 1962) or with measures of resistance to competition from other reinforcers such as food and shock avoidance (Valenstein & Beer, 1962). At high intensities, for example, response rate usually declines because motoric side effects of the stimulation disrupt performance, but animals may choose those intensities over a lower amplitude stimulation that supports a higher response rate.

Hawkins and Pliskoff (1964) have confirmed these findings recently with a new technique. These authors have employed a two-member behavioral chain in which responses on the first lever were reinforced on a variable-interval schedule with the insertion of a retractable lever. Responses on the retractable lever provided brain-stimulation trains on a continuous reinforcement schedule. A comparison of the rates on the two levers revealed that response rate on the first lever continued to increase at stimulus intensities higher than those which produced peak response rates with continuous reinforcement. It was concluded that brain stimulation could not be assessed adequately by self-stimulation rates with continuous reinforcement.

Logically, there are also difficulties. When average response rate is used as a measure of the value of the reinforcer to the animal there exists an implicit assumption that reinforcement strength is homogeneous throughout the testing session. This assumption can not always be met with brain stimulation as some effect of the stimulus which persists may change the value of the reinforcer after its administration. The finding that seizure activity is frequently associated with reinforcing brain stimulation (Newman & Feldman, 1960; Porter, Conrad, & Brady, 1959) suggests that some aspect of the stimulation may persist and obviate the necessity to respond immediately. Equally likely is the possibility that a second stimulation may result in a qualitatively different experience if sufficient time has not elapsed.

Some data collected in our laboratory is pertinent to the point. It has been observed repeatedly that animals with septal electrodes characteristically

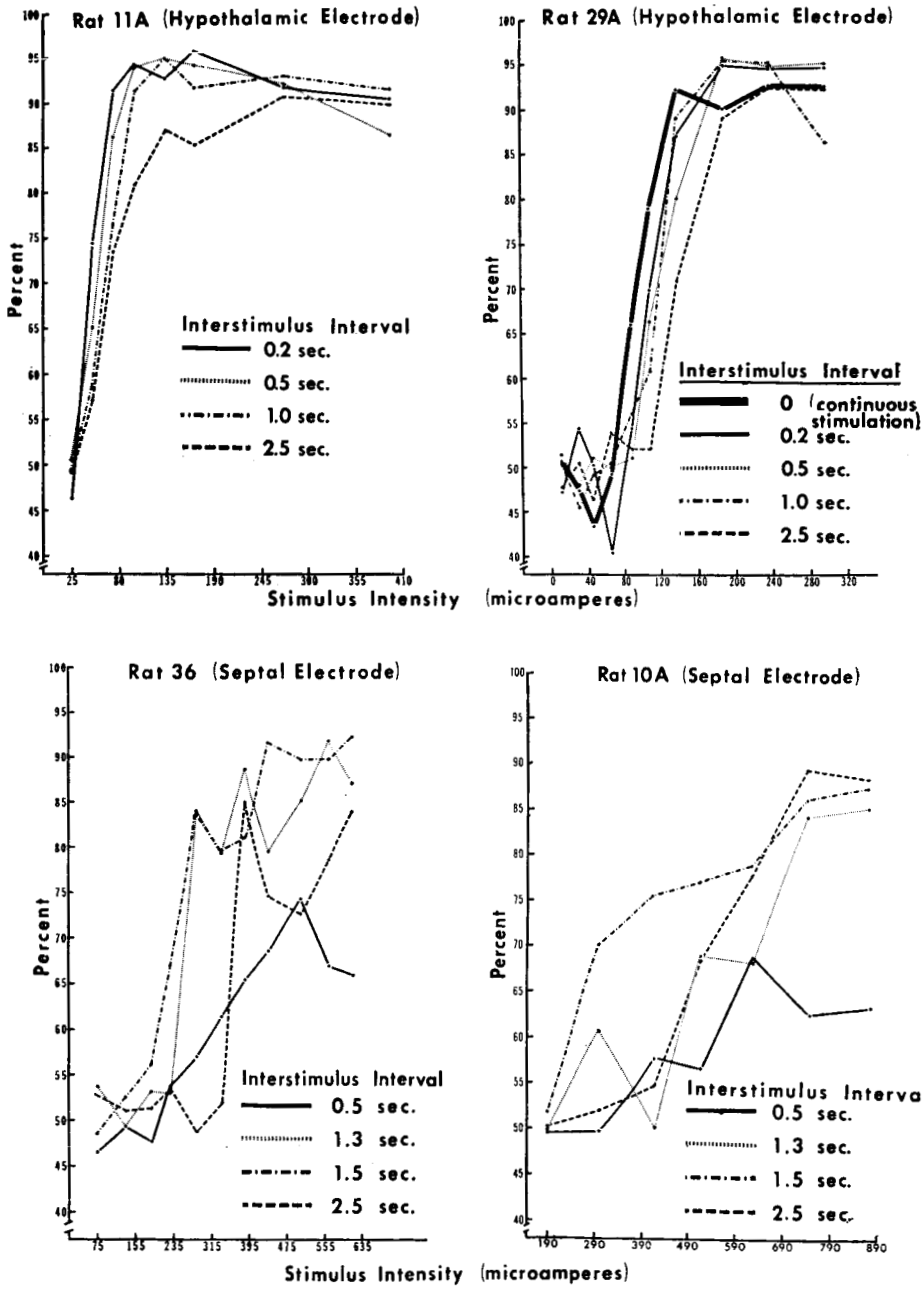

FIG. 1. Comparison of percentage of total time on the positive platform with different stimulation rates (after Valenstein & Meyers, 1964).

stimulate themselves more slowly than do those with electrodes in the posterior hypothalamus. With the self-stimulation procedure animals have control over the rate of stimulation and interpretations of the meaning of

such response rate differences are equivocal. Some light was thrown on the question by a procedure in which the experimenter could vary the rate of stimulation (Valenstein & Meyers, 1964). Rats were placed in a two-platform chamber in which brief trains of brain stimulation were presented when the animal was on the positive (stimulation) platform. As the positive and neutral (no-stimulation) platforms were interchanged on a random schedule, the time spent receiving stimulation provided a useful measure of the animal's orientation to the stimulus.

Figure 1 presents the results of varying the stimulation rate to different reinforcing sites. Percentage of total time which was spent on the positive platform is plotted as function of stimulus intensity. The 50% line represents chance. With hypothalamic stimulation there was no tendency for the animal to leave the positive platform at the fastest stimulation rates; with septal stimulation, however, time on the positive platform decreased with the shorter interstimulus intervals. The septal animals maximized their time on the positive side of the chamber when the stimulus was delivered at a rate approximating that achieved through self-stimulation.

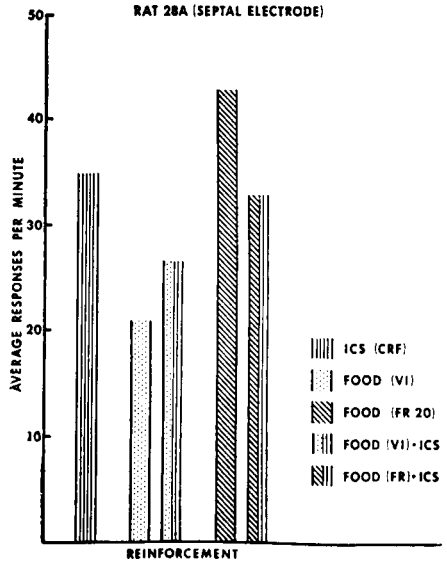

FIG. 2. Average response rate for brain stimulation and food reinforcement presented separately and together.

Several conclusions may be drawn from this data, but what is most relevant to this discussion is that animals receiving septal stimulation respond more slowly than those receiving hypothalamic stimulation because faster stimulation is avoided. The value of the reinforcer to the animal apparently changes following stimulation. Estimates of reinforcement strength based only on response rate are not justified as it appears that with septal stimulation (and perhaps other reinforcing areas) effects of the stimulation may persist.

A similar point may be made with other data from our laboratory. The lever-pressing rate for septal stimulation alone and when combined with food reward on two different schedules of reinforcement was obtained. Animals were food deprived and response rates were obtained independently for septal stimulation on a continuous reinforcement schedule and food reward available at variable intervals. Then the two schedules were combined so that responses on a single lever were reinforced continuously with brain stimulation and at variable intervals with food. If reinforcement strength alone determined rate, response frequency would have increased. Figure 2 shows that actually the rate was lower than that obtained with brain stimulation alone probably because of loss of responding time during eating. A more striking demonstration was obtained when the animal was placed on a schedule requiring 20 responses for each reinforcement

(fixed ratio). Although this schedule generates a fast rate of responding, combining the food reward with brain stimulation resulted in a rate slower than that obtained with food reward alone (Fig. 2). The argument that brain stimulation may have decreased the value of the food reward is mitigated by the observation that the animal always ate the food when it was available. In view of the results obtained on the dual platform with different stimulation rates, it would seem that septal stimulation exerted a braking action on response rate because faster stimulation was unacceptable.

An experiment in which septal stimulation was administered at each contact with a drinking tube containing glucose also supports this interpretation (Asdourian, 1962). Changes from base-line data indicated that the addition of septal stimulation reduced the amount of glucose consumed. It was concluded that a "limiting mechanism" was operating which held the number of stimulations (and necessarily contact with the glucose solution) to about the pretest bar-pressing rate for brain stimulation alone. It should be apparent that an appraisal of the motivational consequences of brain stimulation by determining whether the addition of this reinforcement increases or decreases response rate for food may be misleading (Nielson, Doty, & Rutledge, 1958).

Brain stimulation may also have aversive consequences (Delgado, Roberts, & Miller, 1954), but different techniques are required for measuring the strength of the aversion. A rate measure as used with positive reinforcers is not possible as animals will not respond for aversive stimulation. However, by changing the procedure so that stimulation is postponed for a fixed period of time following each response, an avoidance (or escape) rate may be obtained. To determine the significance of this response rate, it may be necessary to take into consideration the matter of acceptability of faster stimulation rates. In a recent study, stimulation was presented in trains of .5-second duration at the rate of one train per second and a lever press postponed stimulation for 4 seconds (Olds & Olds, 1963). Response rates to postpone stimulation indicated an avoidance tendency, while self-stimulation performance indicated the presence of positive reinforcement. With pure negative reinforcement the results were unambiguous, but with mixed approach-avoidance (ambivalent) effects interpretation was complicated. Some septal electrode placements, for example, were classified as ambivalent because the animals both self-stimulated and responded to postpone stimulation. Considering the previous discussion it seems likely that with slower rates of stimulation these animals may not have terminated the stimulus. Olds and Olds were aware of this problem and wrote:

> In approach tests, the response rates of ambivalent rats were never above one response every two seconds. Thus it appears that in this case, applying the stimulus too often has avoidance effects [p. 277].

Full appreciation of this problem places the "aversive" aspects of stimulation in the so-called ambivalent areas in a different perspective. Only stimulation at fast repetition rate is avoided. As we have little basis by which to evaluate the repetition rate of physiological stimulation, the motivational consequences of activation of such neural structures is questionable.

It would appear that many of the difficulties of a rate measure would be eliminated by providing brain stimulation less frequently than with each response. With such methods, both the disruption of performance by motoric

side effects and the preference for slower stimulation rates would have less influence on response rate. Indeed, the demonstration that intermittent brain stimulation was capable of maintaining behavior was accompanied by the suggestion that this would minimize the influence of gross motor effects of the stimulus on the response rate (Sidman, Brady, Boren, & Conrad, 1955). In view of this advantage of intermittent reinforcement schedules, it might seem strange that regular reinforcement continues to predominate. A partial explanation may be found in the difficulty of maintaining the behavior of many animals with only intermittent brain stimulation. Perhaps comparable is the observation that some animals which press a lever repeatedly for continuous reinforcement do not perform adequately in a simple maze or runway where reinforcement rate is less frequent (Newman, 1961; Olds, 1956; Spear, 1962). There may be a species difference in this respect, as monkeys have been shown to respond stably on fixed ratio schedules requiring 100 responses for one reinforcement (Brodie, Moreno, Malis, & Boren, 1960). In the past, however, brain-stimulation studies with rodents have used only schedules providing a high reinforcement rate which is in striking contrast to the routine testing with ratios of 100 or more with food reinforcement (Ferster & Skinner, 1957).

Recently, however, Pliskoff and Hawkins (1964), using the technique described above, have been able to obtain stable data from rats with schedules providing a low frequency of reinforcement. It will be recalled that these authors use a procedure in which animals are required to press one lever which is reinforced on some schedule with the insertion of a retractable lever. The animal may then receive a brain stimulation train for each response on the retractable lever up to some predetermined number of presses before this lever is withdrawn. With this procedure it has proven possible to maintain behavior on the first lever with variable-interval reinforcement schedules up to VI 4 minutes and fixed ratio schedules up to FR 200. Although this method does not appear equally successful with all reinforcing neural sites, it does suggest that the response rates on the first lever may provide very useful information for assessing the value of the stimulation.

Some caution in using response rate even with intermittent reinforcement should be observed. While response rate appears to reflect the incentive value of the stimulus, it may not similarly reflect internal states of the organism which would be expected to interact with reinforcement value. With food reward, for example, it has been shown that response rate maintained by a variable-interval schedule of reinforcement may be insensitive to deprivation level. Also following repeated testing with fixed ratio schedules, reinforcement may become associated not only with the response, but also with a particular rate of responding. Under these conditions, rate may become an essential part of the response and changes in reinforcement value may not be reflected in response rate (Sidman, 1960). Response rate develops a tempo or rhythm and becomes increasingly stable, but at the same time it is likely to become less sensitive as a measure. The paradox is that until there is a satisfactory independent measure of reinforcement strength, it will be impossible to determine how faithfully response rate reflects reinforcement value. With food reward, the assumption that reinforcement increases with deprivation or quantity of food has common sense appeal. With

brain stimulation there are few convenient guides as manifested by conflicting opinion on the effect of increasing stimulus intensity on reinforcement value (Hodos & Valenstein, 1962; Reynolds, 1958).

Tests which permit an animal to demonstrate a preference may provide a relative measure of reinforcement strength. These tests may consist only of presenting two reinforcing conditions simultaneously and recording some index of the animal's preference. Quantification of the strength of the preference may be accomplished with techniques which require that the animal perform some work in order to change from the less preferred to the more preferred reinforcement. By adjusting the amount of work to a point of equal preference, an estimate of the degree of preference may be achieved. Verhave (1963) has described some of the experimental variables and mathematical considerations applicable to this type of testing procedure when used with food reward. In general, however, preference tests tend to become cumbersome when a large number of stimuli are to be compared. For most experimental purposes, it would be more convenient if reinforcement value could be expressed in terms of a metric unit that would indicate relative position on a scale. Preference tests, however, may help to validate a method which does provide such information.

Tests other than response rate may provide a useful unit of measure. One avenue which has been explored is based on a determination of how much an animal will overcome to obtain reward. Obstruction-box techniques (Warden, 1931) have been generally rejected because of the variability of behavior resulting from repeated electric shock. Recently a test was described in which the number of lever presses required for successive reinforcement increased by a fixed ratio (Hodos, 1961). The measure of reward strength resulting from such a "progressive ratio test" is the number of unreinforced responses an animal will make before the behavior is extinguished. This technique appears to be useful with food reward, but only preliminary information exists with reinforcing brain stimulation (Hodos, 1963). The method has the advantage of eliminating the problems inherent with a response-rate measure and also provides a unit useful for comparative purposes. It will be important, however, to determine if all self-stimulating animals perform reliably under conditions which provide only intermittent reinforcement.

Another measurement problem about which much interest has centered concerns the changes in reinforcement value as a function of the duration of stimulation. When given control over stimulus duration, animals will terminate positive stimulation. This has been attributed to the excitation of a neighboring aversive neural system through a temporal summation of inadequate stimuli (Stein, 1962a). The most frequently used method of obtaining preferred duration permits the animal to hold a single lever down to obtain stimulation which is terminated when the lever is released (Bower & Miller, 1958; Stein, 1962a). This method yields very brief "preferred" durations, but it would appear that the influence of motoric side effects of the stimulation have not been considered sufficiently. Very different data are obtained when animals are not required to hold the lever, but are free to move about the testing chamber until they press a second lever which terminates the stimulus. Direct observation of the behavior suggests that the different results are due to the in-

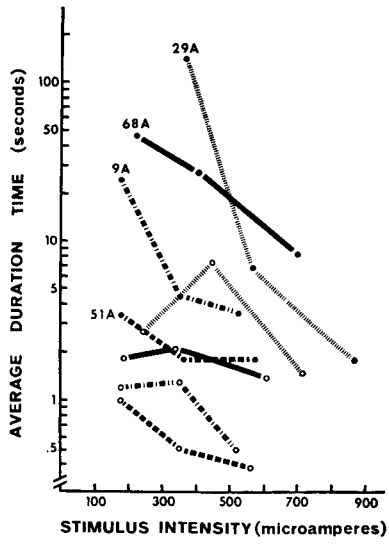

FIG. 3. Comparison of average duration animals maintain brain stimulation when obtained with one-lever (open circles) and two-lever (filled circles) techniques.

ability of the animals to inhibit motor reactions forcing them off the lever, which in the one-lever test terminates the stimulus.

Figure 3 contrasts the results from these two methods with four animals receiving reinforcing hypothalamic stimulation (Valenstein & Valenstein, 1963). It is evident that the preferred durations obtained by the two methods are of different orders of magnitude and are not to be explained away by the fraction of a second necessary to traverse the short distance between the levers. The interpretation suggested by one set of results does not seem to be appropriate to the other. The notion of activation of an aversive system through temporal summation may be appropriate to durations in the order of 1 second, but would require a considerable extension of the neurophysiological data to be applied to durations above 10 seconds.[3]

[3] Temporal summation is generally explained by the addition of excitatory post-synaptic potentials (EPSP). These potentials reach a peak in a few milliseconds and thereafter rapidly decay. Afferent subthreshold volleys, for example, are unable to generate an impulse unless the interval between volleys is less than 5 milliseconds (Eccles, 1957).

Speculation (Miller, 1957) that there exists a unitary neural system underlying all reinforcement which is constantly being modulated by separate drive states has been the impetus for much research. Those neural areas which animals will stimulate themselves are viewed as the best candidates for this unitary reinforcing system. The possibility that activation of drive states may alter the level of excitability of the neural tissue crucial to self-stimulation behavior is implicit in this theory. There is indeed some support for this idea as it has been reported that ingestion of nutrients may change the activity of cells in hypothalamic nuclei (Anand, Chhina, & Singh, 1962; Anand, Dua, & Singh, 1961). Food deprivation also has been shown to increase self-stimulation rate (Brady, Boren, Conrad, & Sidman, 1957; Hodos & Valenstein, 1960; Olds, 1958), but these studies raise a methodological question that is basic to experiments of this design. Figure 4 presents self-stimulation rates of animals when sated and hungry. It can be seen that there are striking differences under the two conditions, but the response rates are considerably below the level of 30 to 100 per minute commonly observed with reinforcing brain stimulation. It becomes necessary to ask whether the stimulation was actually reinforcing at the intensities used to demonstrate these differences. This question is especially critical in view of the well-established relationship between food deprivation and activity level. Activity changes occur not only with food deprivation, but with the administration of depressant

and excitant drugs as well as with stimulation of some neural structures. For example, recently stimulation of the caudate nucleus of the cat (a suggested reinforcing site) has been shown to produce hyperactivity which with some testing procedures may be confused with reinforcement (Justesen, Sharp, & Porter, 1963). Before a rate change can be attributed to any direct effect on the neural substrate of reward, the influence of general activity level on performance must be parceled out as it has been shown that even in the absence of stimulation, food-deprived animals respond at significantly higher rates than sated animals (Hodos & Valenstein, 1960).

THRESHOLD DETERMINATION WITH REINFORCING BRAIN STIMULATION

There are several reasons why the determination of a stimulus intensity threshold is important with brain-stimulation experiments. Self-stimulation behavior would be expected to be most sensitive to influence at low intensities. Presumably, this is true because changes in the excitability of the nervous tissue are likely to have significant influence only if the stimulation intensity is not so high that it overcomes all differences in nerve cell responsiveness. The general acceptance of this point of view can be seen in Stein's (1962c) statements, "drugs effective against depression should increase the ability of the brain to respond to positive reinforcement, either by directly stimulating or sensitizing reward centers, or by selectively inhibiting aversion centers [p. 298];" and "It would be hard to exaggerate the importance of using threshold-intensity currents for these tests [p. 299]."

Threshold determination is also important for charting the reinforcing conseqences of stimulation of different neural areas as it is reasonable to assume that the threshold reflects prox-

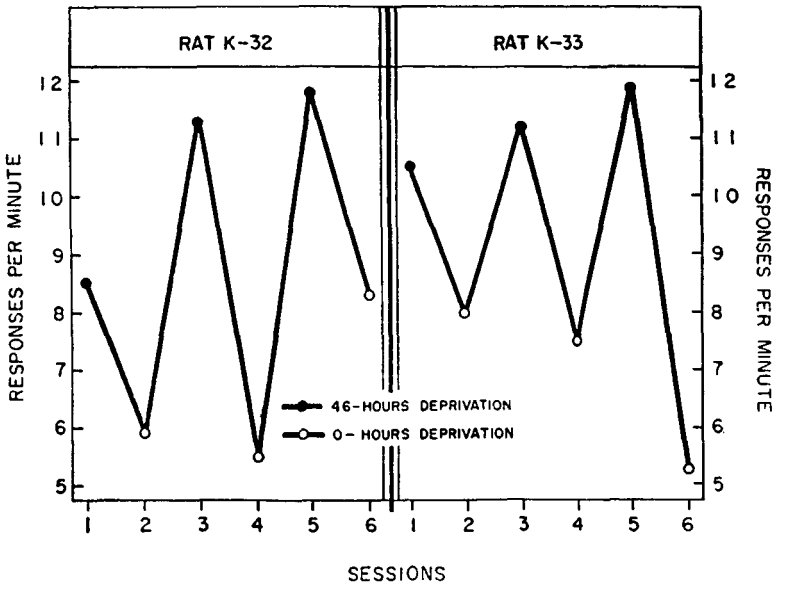

FIG. 4. Lever-pressing rates for intracranial electrical stimulation reward in the two rats as a function of deprivation interval (after Brady, Boren, Conrad, & Sidman, 1957).

imity to the reinforcing site. In addition, the threshold intensity provides some indication of the relative size of the neural field which must be excited in order to achieve effects.

Actually the stimulus threshold has several possible meanings and it is essential that these different meanings be kept separate. Proceeding from the low end of the intensity scale upward we may speak of the cue or detection property of the stimulus, and the lowest intensity which can be sensed, directly or via some mediating process, may be called the *detection threshold.* The animal perceives the stimulus and can be trained to respond to the brain stimulation as to any other discriminable stimulus, but prior to learning, the stimulus is neutral and possesses no special reinforcing consequences. At higher intensities we may speak of a *reinforcement threshold,* which is the minimum intensity capable of maintaining some instrumental behavior to obtain or escape from the stimulus. With appropriate techniques it is possible also to determine *intensity preferences.* This is the intensity the animal selects with a procedure permitting self-regulation. In addition, there are a number of other kinds of reactions associated with stimulation for which thresholds may be determined. These include stereotype motor reactions, the occurrence of convulsions and physiological responses such as cardiovascular changes. An independent variable may affect one threshold but not others, and unless the factors controlling behavior in a particular testing situation are determined, conclusions may be misleading.

The evidence that there is a range of intensities below the reinforcement value that may be detected comes from several directions. It was noted in our laboratory that when the intensity was switched to a low value, experienced rats and guinea pigs stopped responding after only one exposure to the stimulus. In contrast, if the stimulator was turned off, the animal typically responded 15 or more times before there was any interruption of a response rate. Evidently the low intensity stimulation was serving as a cue or signal for the beginning of a nonreward period. With no stimulation at all, the situation was more ambiguous. Recently, the quantitative relationship between the detection and reinforcement thresholds has been investigated by using intensities too low to maintain self-stimulation to signal the availability of reinforcing stimulus intensities (Campbell, 1963).

Stimulation intensities in the reinforcement range also have cue properties. This was demonstrated in an experiment in which positive stimulation served as a conditioned stimulus for an avoidance response (Mogenson & Morrison, 1962). Results with avoidance conditioning also suggest that electrical stimulation of any brain structure provides a distinctive cue to the animal regardless of any other effects associated with the stimulus (Nielson, Knight, & Porter, 1962).

The distinction between detection and reward threshold is equally important with aversive brain stimulation. In determining the threshold intensity for an aversive stimulus it was noted that the subjects (monkeys) were responding to the cue properties of the stimulus (Boren & Malis, 1961). In this testing procedure, an animal's response reduced the intensity of an aversive stimulus that was otherwise increasing at the rate of one step each second. The monkeys started responding when the stimulus reached a certain intensity and thereby prevented the stimulus from increasing above that point. It was first thought that this point indicated the aversive-stimu-

lus threshold, but with additional experimentation it was recognized that as the intensity gradually increased, nonaversive stimuli were playing the role of signals which warned the animal of the forthcoming aversive stimuli. That animals were responding to the warning signal rather than to the aversive stimulation was shown by decreasing the maximal current. In this way it was possible to extinguish responding to the warning signals by separating them from the truly aversive stimuli.

It can be seen that any procedure which employs a regular order of presenting stimulus intensities may distort the reinforcement threshold. Estimates of the reinforcement threshold based on response rate are particularly likely to be distorted when the stimulus intensities are presented in a systematic pattern. With an ascending order, response rate may increase when the stimulus is detected because this serves as a signal for forthcoming reinforcement. This is similar to the well-established finding that with fixed intervals between reinforcements the response curve is "scalloped" (J function) due to the acceleration of rate as the reinforcement time approaches (Ferster & Skinner, 1957). Response rate in the range of intensities between the detection and reinforcement thresholds may reflect *anticipation* of reinforcement, but this is not equivalent to a *response* to a reinforcing stimulus. Anticipatory behavior may reflect general activity, as suggested above, and may also be influenced by a change in sensation threshold. As little is known concerning the mechanism by which animals detect the presence of the stimulus, it is evident that caution should be exercised before attributing a change in rate to a change in sensitivity of "reward" or "aversion" centers.

In contrast to a systematic sequence, a random sequence of intensity presentation yields data that are quite variable, as response rate produced by a given stimulus intensity is influenced by the intensity of the preceding stimulus. If the preceding intensity is high the response rate is likely to be significantly lower than that which would have been obtained with less intense preceding stimuli. Some preliminary data from our laboratory indicate that such effects may persist for as long as 30 minutes. It is not clear whether these results are due to an emotional reaction to the contrast in reinforcement strength or to some change in the responsiveness of the neural tissue following intense stimulation. We will raise this problem again, but at this point we would indicate that while a random presentation of stimulus intensities eliminates anticipatory behavior, it has the drawback of increasing variability.

Many of the problems discussed are exaggerated by a testing procedure which presents a series of intensities during a single testing session. The influence of both the cue properties of the stimulus and contrast effects due to differences in reinforcement strength are minimized when each session offers only one stimulus condition. Even under these conditions, however, it is difficult to make precise estimates of the reinforcement stimulus threshold from curves depicting rate as a function of stimulus intensity. The main problem is that criteria for distinguishing between sub- and suprathreshold performance are difficult to establish.

Figure 5 illustrates this difficulty and also compares results based on response rate with a time measure obtained from the two-platform test previously described. The similarity of the curves obtained with the two techniques supports the position that

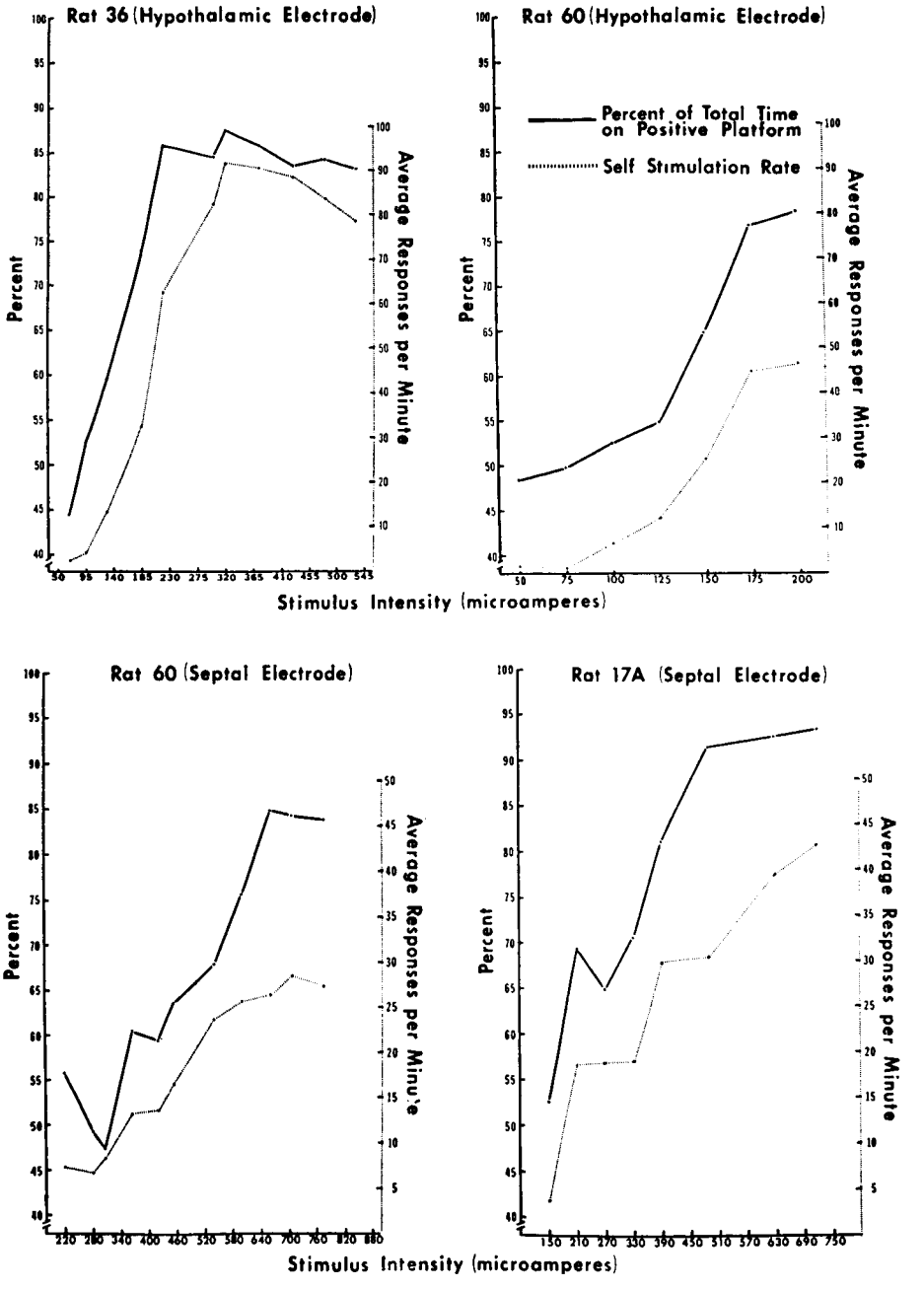

FIG. 5. Comparison of self-stimulation rate and percentage of total time on the positive platform with reinforcing hypothalamic and septal stimulation (after Valenstein & Meyers, 1964).

the same phenomenon was measured. However, it is instructive to compare the relative ease of determining the reinforcing stimulus threshold. With the two-platform test the positive (stimulation) and neutral platforms are switched on a random sequence throughout each test. As 50% of the total testing time on the positive platform represents chance expectancy, performance deviating from chance may be evaluated statistically. With self-stimulation rate there is no convenient standard against which to evaluate a specific rate. Response levels prior to stimulation experience (operant behavior) do not provide a useful criterion as it has been shown, for example, that even with one food-reinforced session, rates may consistently remain above previous operant levels (Segal, 1962). Also, after experience with reinforcing brain stimulation, we have noted that response rate remains significantly above "operant levels" during extinction trials.

Figure 6 illustrates that the response rate during the first two extinction tests averaged over 500% of the previous operant level. By the tenth test the rate had appeared to stabilize at approximately 200% of operant level. On the eleventh trial, the introduction of a 5-minute period of brain stimulation at the end of the 20-minute extinction session caused the rate to rise even in the nonstimulation period. Rate gradually declined with successive tests presumably as the animal learned that reinforcement was available only after 20 minutes. It would be anticipated that if reinforcing stimulation were introduced at random intervals, the rate during the

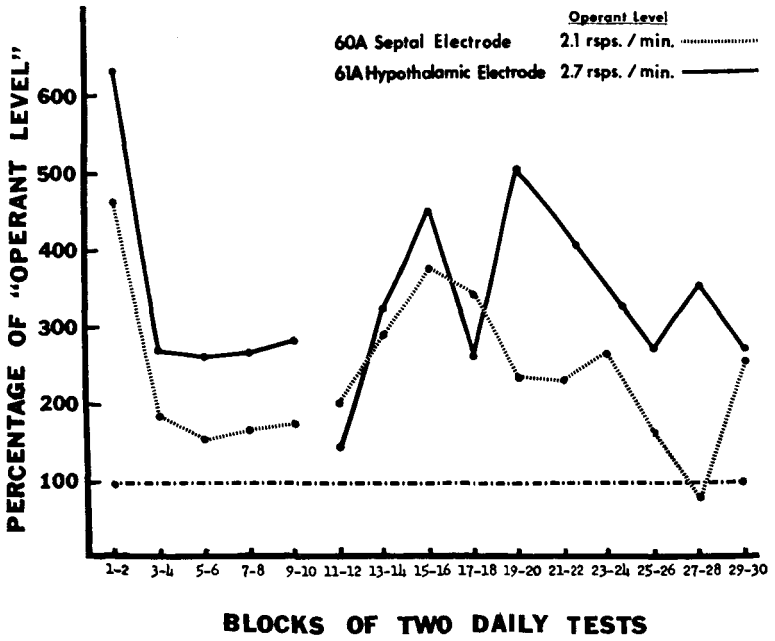

FIG. 6. Percentage of "operant" response level during extinction test following reinforcing brain stimulation. (Each point represents the average of two 20-minute daily tests. On Day 11 a 5-minute brain stimulation session was given following each 20-minute extinction period.)

extinction periods would have remained even higher.

This tendency toward higher response levels following a history of association with reinforcement illustrates the difficulty in estimating the reinforcement threshold precisely with a rate measure. It may be possible to obtain a daily operant level in order to compensate for this tendency toward increased response rates. For some purposes this method may be adequate, but in actual practice it will often be difficult (without an extensive investigation) to decide whether operant behavior should be sampled before, during, or after each test session.

After the animal has become familiar with the procedure, the reinforcement threshold obtained with the two-platform technique does not change with additional experience (Valenstein & Meyers, 1964), but there remains a possibility of an interaction between the cue and reinforcement properties of the stimulus. Animals may seek out stimulation at subreinforcement intensities as a result of a generalization gradient based on the cue properties. This is an empirical question which may be answered by offering animals stimulation only at the questionable intensities without any additional experience with higher intensities. Under these conditions extinction would be expected if stimulation was not reinforcing in its own right.

Other methods have been used to assay the excitability of the neural substrate underlying reinforcement. Most noteworthy are two interesting procedures which permit animals to self-regulate the intensity. The original technique introduced a method for determining the preferred intensity of stimulation (Stein & Ray, 1959). Animals were trained to press either of two levers to receive a brief reinforcing stimulus, but responses on one lever produced stepwise increments in intensity, while the other lever produced equal decrements in intensity. Current levels were started at zero and a trained animal increased the current level by responding on the appropriate lever and then by alternating between levers, maintained the intensity around a "preferred" level. This technique was apparently abandoned because many animals did not provide stable data. Current regulation was more reliable with posterior (hypothalamus and midbrain tegmentum) electrode placements, while rostral sites (septal area) produced poor regulation as animals often increased the intensity until convulsions occurred. In spite of this shortcoming, several interesting facts emerged. According to Stein and Ray (1959), preferred levels, for example, were usually higher than "experimenters would care to assign under the conventional fixed-intensity procedure. Exaggerated and even violent motor activity was often produced by the intensities selected . . . [p. 571]." Motor activity at the preferred intensity would be expected to depress self-stimulation rate. This finding further questions the validity of a rate measure and supports the observation that animals often prefer very high stimulus intensities over more moderate intensities which may produce higher rates of responding.

The second self-regulatory technique has been explored more extensively (Stein & Ray, 1960) and has yielded more stable results and considerably more information particularly with respect to the action of drugs. This method also employs two levers, but brain stimulation is received as a consequence of pressing only one of them. With each successive stimulus presen-

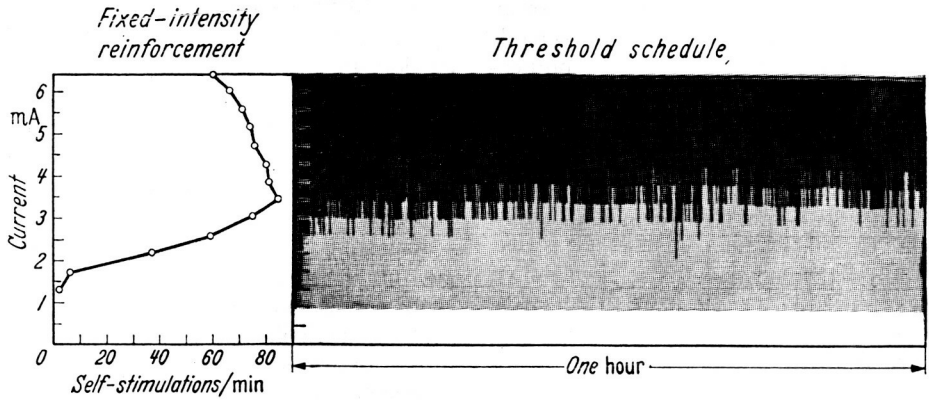

FIG. 7. Comparison of two indexes of the threshold for brain-stimulation reward: (left) self-stimulation rate obtained with fixed-intensity reinforcement versus (right) current intensity at reset in threshold schedule. (The horizontal markings to the left of the threshold record indicate the 16 current levels—15 steps—available from 6.4 milliamperes to zero milliamperes. In the 1-hour period shown, the animal gave himself 4,247 brain shocks and reset the current 558 times. After Stein and Ray, 1960.)

tation, the intensity is decreased in small steps, but at any time the animal may reset the intensity to the initial high level by pressing the "reset" lever.

The step at which the animal resets the intensity tends to be reliable and sensitive to stimulus parameters and administration of drugs. It does not represent, however, the lowest intensity that will provide reinforcement (Stein, 1961). Figure 7, for example, illustrates that high self-stimulation rates may be obtained at resetting intensities. One possible explanation is that the cue properties of the stimulus enable the animal to "anticipate" a drop in reinforcement value. Several alternative explanations are possible, but it is important to stress that this technique yields a "threshold" that is significantly higher than the reinforcement threshold as it is commonly defined.

There is one shortcoming of this procedure and one major question of interpretation which should be considered in view of the quantity of data derived from this approach. As with the self-regulatory method for preference threshold, this procedure does not appear to be useful with all reinforcing sites. To date, published studies include only electrode placements in the hypothalamus and tegmentum. In our laboratory attempts to obtain reliable data with reinforcing telencephalic sites have been unsuccessful. With septal placements, for example, animals tend to press more and more slowly with decreases in current level and often self-stimulation behavior is extinguished before the intensity is reset. This may be explained by the relatively rapid extinction reported with septal stimulation (Seward, Uyeda, & Olds, 1959), but the inability to use this procedure with many reinforcing areas limits its value particularly as a method for locating action sites of drugs.

Interpretively, changes in resetting level following administration of drugs have been attributed to either changes

in excitability of the specific brain structures stimulated by the electrode or more conservatively to a modification of a positive reinforcing system. In order to understand any change brought about through the introduction of an experimental variable, it is important to determine what factors control the behavior in the test situation under analysis. It has been shown that the resetting intensity is sensitive to stimulus parameters, and even shifts from stimulation rates of 25 to 33 cycles per second may be discriminated (Stein & Ray, 1960). However, other variables in addition to the stimulus parameter-neutral excitability dimension may influence behavior in this situation.

In a test requiring repetitive acts, behavior generally develops a rhythmic pattern. In this particular test, for example, it may be observed that animals emit a regular number of responses on the stimulation lever, then press the reset lever and repeat this sequence over and over again. Any experimental variable that modifies this pattern will have an effect on the resetting intensity. Drugs such as amphetamine, pentobarbital, chlorpromazine, and reserpine which have been shown to alter resetting intensity have a number of both central and peripheral effects which may modify this behavior pattern other than through a presumed sensitization or depression of a reward system. The finding that amphetamine lowers the resetting intensity, for example, is viewed as resulting from facilitation of the hypothalamic reinforcing system (Stein, 1962b). The possibility that amphetamine induced a nonspecific motor activation was evaluated by testing animals in a conventional lever-pressing situation. Amphetamine increased response rates to a "subthreshold" stimulus, but there was no increase in rate if the stimulus was not presented (Stein, 1964a.) Nevertheless, the conclusion that amphetamine effects the "reinforcing system" may be premature. Uyeda and Fuster (1962), for example, have tested the tachistoscopic performance of monkeys and concluded that amphetamine improved accuracy and shortened reaction time. As similar results were obtained from electrical stimulation of the mesencephalic reticular formation the authors conclude that amphetamine has a reticulotrophic action. These results raise the possibility that it is the perception of subthreshold stimuli which may be influenced rather than the reinforcement process. In any case, a comparison of the conclusions from the two sets of experiments indicate the danger of attributing changes in performance to any specific or assumed neural system.

Amphetamine has been shown to increase the tendency to respond in many different experimental situations with both positive and negative reinforcement (see Carlton, 1963). In one illustrative experiment (Carlton, 1961) rats were required to alternate between two levers in order to obtain food reward. Following administration of amphetamine, "perseverative" tendencies were enhanced. That is, animals tended to repeat responses on the same lever although they received no food unless they alternated. With the self-determination method of obtaining brain-stimulation threshold animals were required to switch from one lever to the other in order to reset the stimulus intensity. Any "perseverative" tendency or enhancement of responding would cause the animal to drive the intensity down to a lower level. It would appear gratuitous at this time to attribute any change in

resetting level to any alteration of specific neural elements.

NEURAL INTERACTION AND REINFORCING BRAIN STIMULATION

Limbic neural pathways have been extensively described, but the determination of the behavioral significance of these pathways lies outside the neuroanatomical discipline. It is necessary to have a behavioral measure which can be attributed to some neural structure in order to evaluate the nature of the interaction between structures. The self-stimulation phenomenon appears to be particularly convenient for this type of analysis as, at least as a first approximation, behavior may be considered to be under the control of the neural structures surrounding the electrode tip.

Through activation (stimulation) or deactivation (ablation or anesthetization) of one of two connecting structures, an indication of the interaction between these structures should be revealed. Using this basic approach some interesting interaction effects between specific limbic systems have been demonstrated, but the significance of the interaction is not always clear. For example, stimulation of the caudate nucleus of a monkey produced a high and stable rate of bar pressing at the start of a session. However, if stimulation of either the hypothalamus or amygdala preceded the caudate stimulation, lever pressing was significantly lower and less stable (Brady, 1961). To interpret such data we must ask whether these findings result from a specific interaction between these nuclei. With food reinforcement, for example, it has been observed that when an animal "anticipates" a particular reward a change in reward value will result in an elevation or depression of activity dependent upon the relationship of the two rewards. It has been suggested that this may result from an emotional reaction to the contrast (Crespi, 1944). It is not unreasonable to expect a similar effect with contrasting reinforcing brain stimulation, and indeed Hawkins and Pliskoff (1964) have reported such effects. Presumably contrast effects also have a neurological basis, but until the mechanisms of emotional reactions are better understood, interpretations which imply specific interactions between brain sites must be regarded cautiously.

Lesion technique may be used to determine whether a reinforcing site may be modified by eliminating the influence of another area. In one experiment the dependence of reinforcing tegmental stimulation on any crucial activity of the septal area or fornix system was tested (Ward, 1960). It was concluded that there was no such dependence, as rats with large lesions in the septal area continued to self-stimulate for tegmental stimuli. Providing the possibility of threshold change is examined, it would seem safe to draw conclusions from such "negative" results. However, where self-stimulation behavior is eliminated or decreased, it is necessary to determine whether the reinforcing properties of stimulation or some performance capacity has been modified. In a recent report it was shown that there were deficits in bar pressing for cingulate stimulation following hypothalamic lesions (Coons & Fonberg, 1963). The conclusion that the hypothalamus mediated reward obtained from cingulate stimulation must be evaluated together with the possibility that hypothalamic lesions affected performance sufficiently to cause a decrease in lever-pressing rate. As a minimum

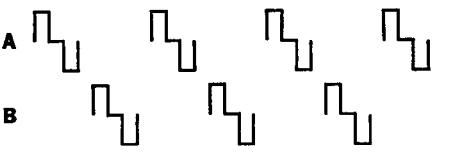

FIG. 8. Method of "simultaneously" stimulating two brain areas without electrical interaction (see text).

control it would be desirable to have a measure of the constancy of performance maintained by a reinforcer independent of brain stimulation.

Where results suggest an inhibitory action of one area on another it is also important to determine whether this action is specific or of a general nature. An example may serve to illustrate this point. There is a considerable body of information supporting the view that feeding behavior is controlled by the interaction of a lateral hypothalamic "feeding center" and a medial hypothalamic "satiety center" (Anand & Brobeck, 1951). As stimulation in the lateral area also provides positive reinforcement while stimulation in the medial area appears to be aversive, it has been suggested that there may exist a similar interaction of reinforcing systems (Hoebel & Teitelbaum, 1962). Indeed, it was demonstrated that when mild ventral stimulation was superimposed upon stimulation of the lateral area the animals stopped lever pressing. However, as medial stimulation is generally considered to have some aversive properties it is not surprising that the addition of a negative reinforcement should result in a lowering of response rate. It would be important to determine the influence of medial stimulation on other reinforcing brain sites (as well as with positive reinforcers other than brain stimulation) before any direct relationship is inferred.

Although studies of neural interaction that use electrical stimulation in contrast to lesion methods have the advantage of reversible effects, there are technical problems which raise some questions about interpretation. When knowledge has been obtained about the response of an animal to stimulation of a given neural area (Site A) there may be interest in changes in response characteristics resulting from stimulating a second neural area (Site B). It is hoped that some information pertinent to the nature of the neural interaction may be inferred by simultaneously stimulating the two areas. Not often considered is the possibility that *the interaction may be electrical rather than neural.* We have noted, for example, that effects characteristic of Site A (e.g., stereotype motor responses) may be triggered by stimulating Site B if a low, subthreshold stimulus is also presented to Site A. This may be true even when the stimulators are electrically isolated from one another and the electrodes located some distance apart. The fact that this effect may be produced when a number of different areas are substituted for Site B suggests that these results should not be attributed to a neural interaction. We do not at present understand the mechanism involved, but could suggest the possibility that overlapping electrical fields which are ineffective by themselves may interact in one of several ways to produce an observable result. In any case the problem may be circumvented. In our laboratory we are using an electronic gating circuit which rapidly opens and closes each electrode-stimulator pathway to prevent nonneural interactions. Figure 8 illustrates this method of "simultaneously" stimulating two sites. Both Stimulation A and B consist of biphasic pulse pairs presented at the

rate of 100 per second, but each circuit is opened only during the presentation of a pulse pair. Other solutions are possible, but when simultaneous stimulation is used to study neural interaction, awareness of the possibilities of nonphysiological interactions should be indicated.

In addition to investigation of interaction between specific neural structures, other studies have dealt with the interaction between systems. Recently suggestions have appeared in the literature that an aversive-reinforcing system may inhibit the positive reinforcing system. In one experiment, rats placed in a shuttle box were permitted 7.5 seconds after the presentation of a tone to avoid aversive brain stimulation by crossing to the opposite side of the box (Stein, 1964b). Animals were slow to learn the avoidance response under these conditions and typically waited until receiving the first stimulation before leaping to escape. However, if a "priming" stimulation of a positive area was presented with the onset of the warning tone, the number of successful avoidance responses increased significantly.

How can these interesting results be interpreted? One way is to postulate an interaction between the positive and aversive neural systems. Such an interaction has been hypothesized by Olds and Olds (1962) with reference to positive lateral hypothalamic and aversive tegmental stimulation:

> the termination of the tegmental stimulus will result in a release phenomenon in the lateral hypothalamic area. That is, there will be an augmentation of neural activity in the lateral hypothalamus on termination of the supposed negative reinforcing stimulus. Now this augmentation may be the sole prerequisite of positive reinforcement [p. 809].

According to this theory, avoidance or escape behavior is not reinforced directly by the elimination of the noxious stimulation, but rather results from releasing the hypothalamic reinforcement center from an inhibitory influence. With respect to the performance of the rat in the shuttle-box situation described above, it has been suggested that the priming positive stimulation lowers the threshold in the hypothalamus and thereby increases the probability of the avoidance response (Stein, 1964b). Although the nature of the interaction is not explicitly stated, there is the implicit assumption that the reinforcement for the avoidance response is channeled through the hypothalamic system.

An alternative explanation emerges from an examination of the somatic concomitants of the stimulus. It can be observed that different motor patterns are brought into play by positive and negative stimulation. With positive brain stimulation animals move forward and appear to be actively investigating the environment. As the response is immediate and the stimulus provides no directional cues, it appears that this motoric response is directly triggered by the stimulation. Negative brain stimulation, provided it is not so intense that it causes the animal to jump straight up, appears to activate a "freezing" or backward movement. This triggering of competing responses (motor inhibition and facilitation) by stimulation of different limbic structures has been the subject of a number of studies (see Kaada, 1951). Behavioral implications of these findings have been studied by McCleary (1961). Where the environment is sensed by cephalad receptors, the evolutionary survival value of such behavior patterns would tend to result in their perpetuation. Noxious stimuli signaling danger elicit

withdrawal patterns; positive stimuli elicit approach patterns.[4]

We are reminded of Guthrie's (1935) advice: "To train a dog to jump through a hoop, the effectiveness of punishment depends on where it is applied, front or rear [p. 160]." Recently, it was demonstrated that runway performance could be either facilitated or inhibited depending upon whether shock was delivered to the hind or forepaws (Fowler & Miller, 1963). It has already been noted that recent evidence has suggested that interoceptive as well as exteroceptive stimulation can directly determine response characteristics.

The motor patterns which are triggered by positive and negative stimulation are antagonistic. The warning tone (conditioned aversive stimulus) presented to the rat in the shuttle box elicits motor patterns which interfere with the forward movement necessary for successful avoidance. The "priming," positive stimulation initiates a forward movement, which improves avoidance performance in this situation. In agreement with this view is the observation that the positive stimulus antagonized the "freezing" reaction to the warning signal and permitted the avoidance response to get started (Stein, 1964b).

It is true that if the motor responses are antagonistic in a sense the underlying neural process may also be viewed as antagonistic. There is, however, an important distinction to be borne in mind. The antagonism of motoric reactions simply recognizes the fact that an animal can not be simultaneously immobilized and moving forward. This does not necessitate any direct interaction between central neural processes. Explanatory theories should take into consideration other alternatives as well as hypotheses that imply interactions within the central nervous system.

[4] For theoretical presentation of processes underlying approach and withdrawal mechanisms the reader is referred to Schneirla, 1959.

CONCLUDING REMARKS

The paper has dealt with problems of measuring the reinforcing consequences of brain stimulation. In illustrating problems there is always the danger of not viewing the progress in proper perspective. Actually much of the work cited has been of a pioneering nature, often extremely rich in hypotheses and frequently very creative methodologically. Subsequent work has attempted precision, but often with the rough implements of the frontier. Conclusions have gone beyond a general statement of possible usefulness of a technique to claims that this drug has this effect for this reason. It therefore seems appropriate and important at this time to examine the methods used to reach these conclusions.

Studies of the reinforcing consequences of stimulation are likely to make significant advances in our understanding of the physiology of such familiar chapter headings as motivation, emotion, drive, instinct, reinforcement, learning, and many others. It is most important that we travel a road which will permit the accumulation of valid conclusions which are meaningful beyond the idiosyncratic conditions of a particular experimental method. The present paper has not constructed any freeways. This has been an attempt to place caution signs where existing roads are dangerous and road blocks where progress is not possible. For the theoretician who attempts to integrate recent findings in this area:

PROCEED AT YOUR OWN RISK!

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